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August 1956

Papers from a conference on

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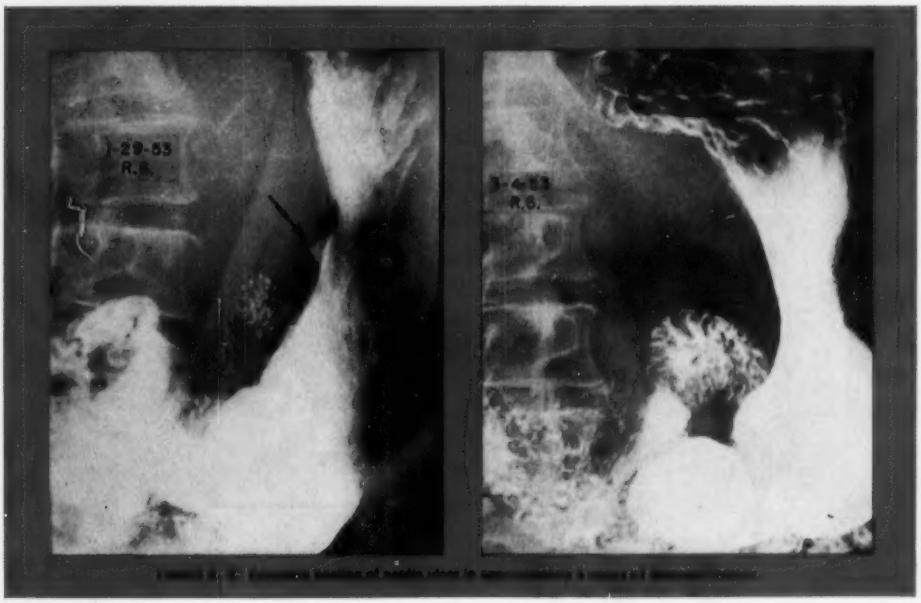

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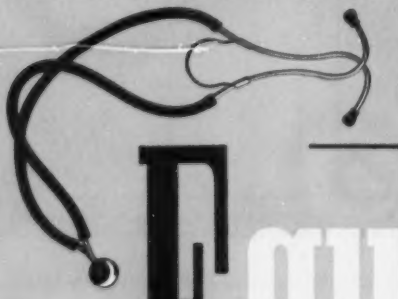

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DIAGNOSIS AND TREATMENT OF NUTRITIONAL DISTURBANCES
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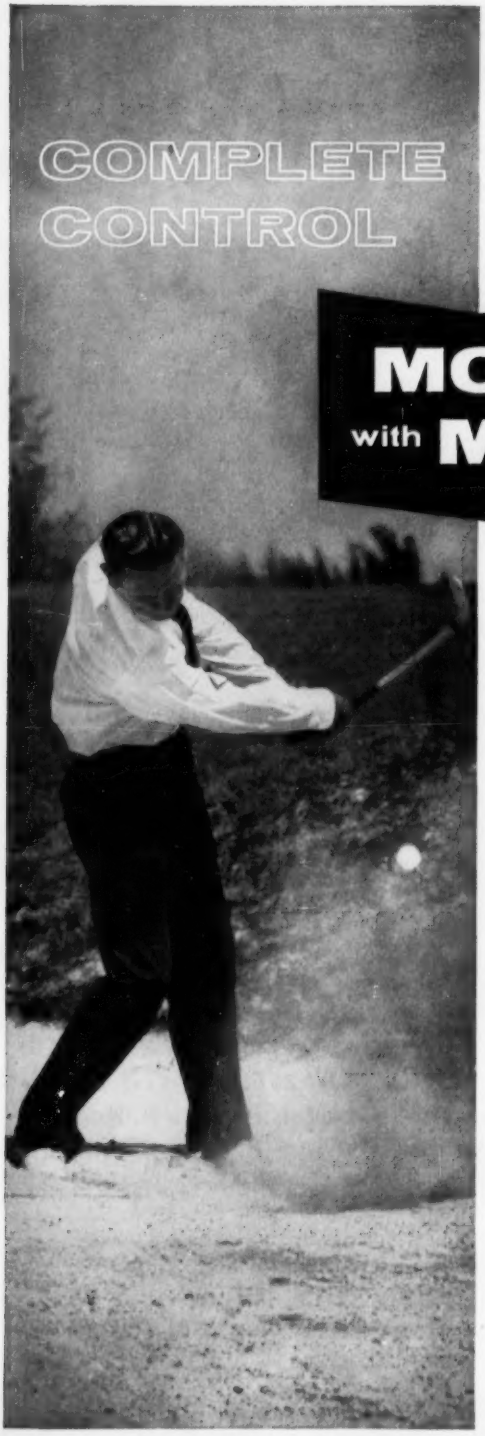

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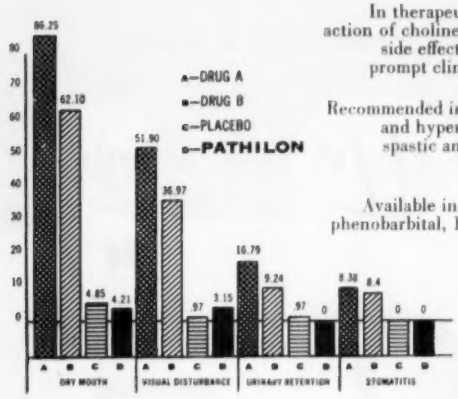

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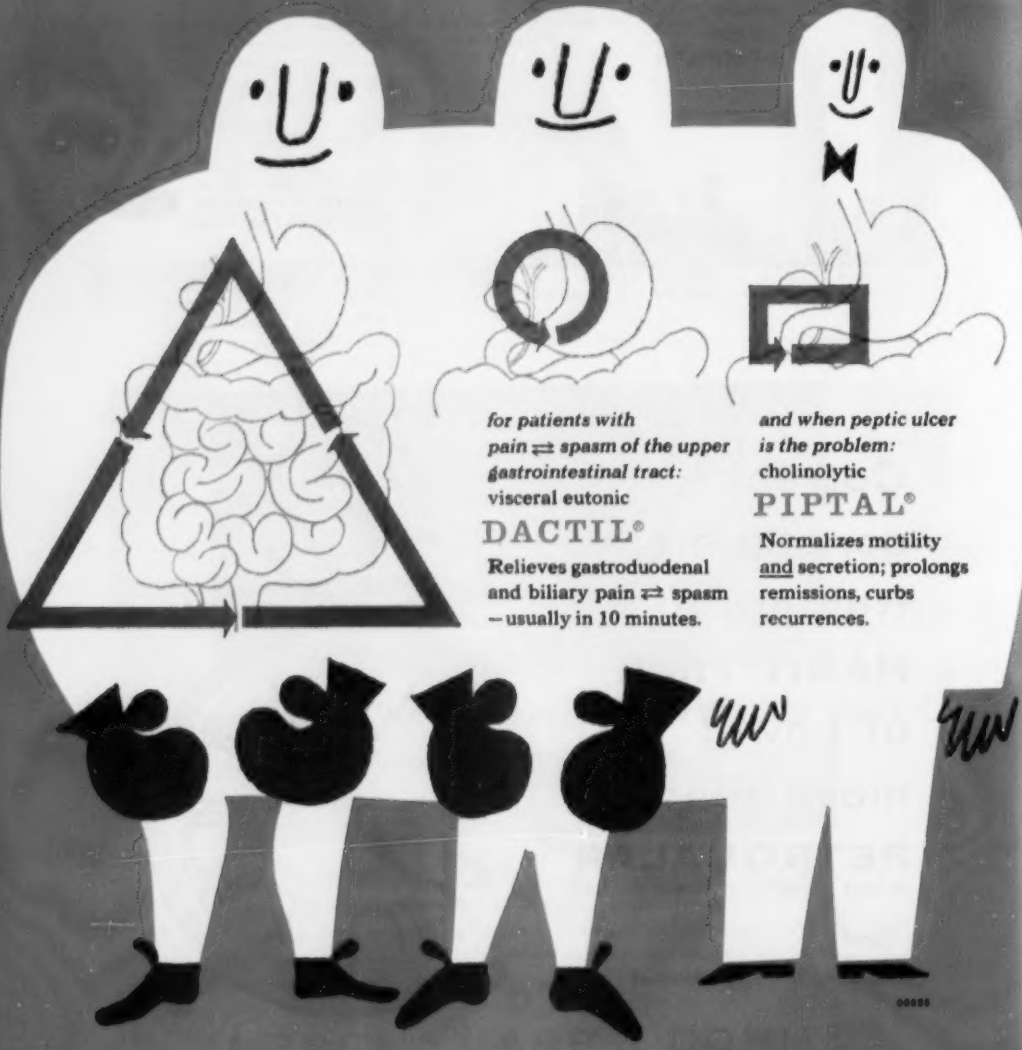

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Diagnosis and Treatment of Nutritional Disturbances

NORMAN JOLLIFFE, M.D.

A NUTRITIONAL deficiency syndrome may manifest itself as a specific entity, such as pellagra, beriberi, scurvy, and the like, or more frequently as a mixture of signs that are not typically characteristic of any single disease pattern. When the latter happens the best designation is usually that of "mixed deficiency syndrome."

A nutritional deficiency syndrome may also be superimposed upon, and may adversely influence, another pre-existing or coexisting disease. Therefore it is necessary also to consider a deficiency syndrome as a complicating factor in other diseases.

Nutritional deficiency diseases may vary widely in their clinical manifestations. The disease may be rapidly progressive, that is, acute in terms of velocity or the speed of development; it may be severe or mild in terms of pathology or dysfunction and its effects on the individual. Deficiency disease can be rapid and fulminating, causing death in a matter of days, or it may be insidious, barely recognizable clinically, yet present and sapping the energy, the ability to work and play, and the general health of the individual involved.

The specific deficiency diseases, the classical disease syndromes, are well known and fortunately are reasonably well treated and guarded against in medically civilized communities. Consequently, classical scurvy, acute severe pellagra, xerophthalmia, rickets, and beriberi,

Presented at a conference on Nutritional and Metabolic Considerations in Disease, held jointly by the Commissions on Nutrition of the Medical Society of the State of Pennsylvania and the Philadelphia County Medical Society and the National Vitamin Foundation, November, 1955, Philadelphia, Pa.

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as specific individual death-dealing or debilitating entities are fortunately of diminishing frequency throughout most of the world today. In some more-favored areas they are practically extinct as public health problems. On the other hand, in certain less-favored areas subacute and chronic or mild to moderately severe forms, especially when they give the nonclassical mixed deficiency syndromes, are often endemic. As a matter of fact, they exist in larger amounts in the more-favored areas than many authorities like to admit. It is wise always to remember that nutritional deficiency disease occurs in all races, at all ages, in both sexes, and in people of all income levels, and is prevalent in varying degrees throughout the world today. The incidence varies from 15 to 20 per cent to practically 100 per cent of the individuals examined, and contrary to a widespread opinion, the upper income groups are not immune. These milder and commonly mixed forms of nutritional deficiency syndromes definitely reduce the level of health and productivity of the individuals involved, and of the groups in which they live. It is well established that deficiency disease and even a nutritional inadequacy without obvious clinical signs, may impair growth, organ and mental development, resistance to many infections, and ability to attain the maximum rate of wound healing; may increase complications of gestation and lactation; and may decrease working ability.

FUNCTIONAL SIGNS

Often the earliest and most frequently missed early deficiency disease syndrome consists of symptoms that are ordinarily regarded as neurasthenic in nature, such as disturbances of sleep, inability to concentrate, heart consciousness, dyspepsia, gaseous eructations, and various unusual bodily sensations.[1] Although these highly nonspecific symptoms may be caused by many factors other than nutrient deficiencies all too frequently their nutritional basis is overlooked and inappropriate treatment used.

Examples of the more objective functional changes resulting from deficiency syndromes that require specific technics for their demonstration are:

- Inability to see in dim light, related to vitamin A deficiency
- Electrocardiographic changes that occur in thiamine depletion and in electrolyte disturbances of potassium
- "Puddling" and other changes in the small-intestine x-ray pattern, related to B-complex deficiencies

Historically[2] the drive to obtain and insure dietary adequacy has caused mass migrations and war. Mild dietary inadequacies, particularly of calories, have provoked peoples either to rebellion or to heroic group effort, depending upon motivation and leadership. Severe food inadequacies have made people angry, submissive, listless, disease-ridden, and incapable of productive work, resistance and, finally, of continuing to live. Entire population groups reduced to the listless stage have subsisted for generations with chronic dietary inadequacies sufficient to progressively lower their work output, which, with high fecundity, results in a constantly diminishing per capita food supply. Keys and his Minnesota group[3] made an important study of the emotional factors in experimental semistarvation during the last world war. This study should be required reading for all those interested in the relationship of nutrition and emotions.

ANATOMIC LESIONS

Anatomic (morphologic) changes become apparent as a rule somewhat later than the functional changes, and may even occur before biochemical aids have altered sufficiently to be diagnostic. Various degrees of these lesions can be detected, according to the character, its duration, velocity, and severity of the deficiency.[2-4] The severe and classical degrees are well known and are infrequently missed. However, the milder and less advanced lesions are frequently overlooked and unrecognized. Often they are so frequent that they are considered "normal" or "natural." Following these lesions, particularly when a stress or conditioning factor becomes operative, the classical lesions rapidly develop. Here, of course, the important point is to recognize these signs, particularly at the beginning of another disease, so as to institute proper nutritional therapy before the milder and earlier signs have a chance of developing into dangerous syndromes.

BIOCHEMICAL AIDS IN DIAGNOSIS

Much less well known than the anatomic lesions are the "biochemical lesions" which not only accompany these anatomic lesions but often precede them as well. In these lesions perhaps lie the fundamental symptoms of deficiency disease at the tissue or cell level, where the influence is directly on the metabolic action of the tissue or enzyme system. Perhaps the best example of an established "biochemical lesion" associated with nutritional deficiency disease is the finding of excess

pyruvic acid in the blood following exercise or the glucose-tolerance test in thiamine depletion.

The value of biochemical aids, in this observer's opinion, seems to have been overemphasized as a diagnostic aid in the individual subject. In this country the medical nutritionists seldom see a patient who has not already been given vitamins which can rapidly reverse many abnormal biochemical findings and give normal blood and urine levels. However, some of the biochemical aids are extremely valuable. I am referring particularly to blood levels of vitamin B_{12} which remain abnormally low in patients with pernicious anemia even when they have been treated with oral multiple-vitamin preparations that do not contain the intrinsic factor. This should prove to be valuable aid in the diagnosis of pernicious anemia before anemia develops, and in the diagnosis of combined-system disease without anemia.[5]

The chief value of the biochemical aids is in nutritional status surveys. Here they serve as a check on the clinical findings[6,7] and furnish a reliable method of estimating the recent dietary intake of nutrients more reliably and expeditiously than do dietary histories.

NUTRIENT RESERVES

In the development of deficiency diseases one of the many variable factors that complicate the evaluation and directly influence the course and prognosis is the status of the body's nutrient reserves. These obviously vary from patient to patient and from time to time in the same patient depending upon the previous dietary intake and the condition of the individual. These nutrient reserves constitute an important safety factor interposed between the occurrence of nutritional inadequacy and the development of deficiency disease. The reserves also function between the variations in the dietary intake and the variations of the metabolic demands of the body itself and in so doing generally make it possible to maintain at a physiologic level the tissue concentration of the essential nutrients.

The reserves vary from nutrient to nutrient. Reserves may be large, as with calcium and vitamin A; several months' normal supply of these two nutrients may be stored in the bones and the liver of a well-fed adult. Or the reserves may be moderate or even relatively small, as in the case of thiamine, wherein several days of total deprivation coupled with a high-calorie intake and large energy expenditure are sufficient to deplete the nutrient reserve. Perhaps the extreme is represented by the reserves of amino acids, wherein the labile supply is but a few brief

hours, after which time normal tissue must be metabolized for the body's supply of nitrogen.

PREVENTION OF NUTRITIONAL DEFICIENCY

In the preceding pages it has been shown that wide variations in the manifestations of deficiency disease exist and that these variations are directly and indirectly dependent upon numerous factors which make the diagnosis of nutritional deficiencies especially in their mixed and atypical forms a medically intriguing problem. The proper diagnosis and evaluation, although often easy, may be highly complex, and represents a challenge to the clinician. Its importance is manifest. The prevention and treatment, therefore, cross all phases of medicine, and of economics, social structure, and activity as well.

National Awareness

At the national level it is constantly important to keep alive the knowledge of the existence of nutritional inadequacies and their significance on the welfare and progress of the nation and the people as a whole. Public-health services should encourage and engage in good nutrition education and the provision of diagnostic and treatment facilities, and should provide for the proper legal and enforcement facilities for enrichment programs and nutritional supplementation programs. Everyone dealing with the problem at a national level should keep alert to varying local situations and help in every way by suggestion, teaching, demonstration projects, and the procuring of necessary diagnostic or therapeutic or preventive supplements when indicated.

Clinical Alertness

At the clinical level, the physician must remain constantly alert to the significance and existence of nutritional deficiency diseases—its protean manifestations, syndromes, and complications—and must constantly press for better nutrition practices on the part of his patients as well as simply prescribing the necessary diets and nutritional therapy.

Fallacious Advice

The physician must be alert to all fallacious promotional claims. He is already well informed against unthinkingly accepting fads, nostrums, and the various nutritional schemes of quacks. However, he is susceptible to unthinkingly accepting at face value economically oriented

nutritional and medical doctrines recommended by some nonmedical scientists, particularly when they are associated with one of our honored universities. Too often one hears from some of them advice which is economically expedient for certain groups but nutritionally and medically unsound for human beings. For example:

"Drink an *extra* glass of milk every day."

In truth, an extra glass of milk can be too much milk, just as extra butter, cereal, fruit, or vegetables can be too much butter, cereal, fruit, or vegetables. Extra food leads either to obesity or to an inadequate intake of other foods and the consequent risk of a nutritional deficiency.

"Some certain foods are essential to health."

Actually, no single food is essential to health. It is the nutrients in foods that are essential, and without exception there are several food sources of every known essential nutrient.

"One must eat only 'natural' foods."

In truth, food processing, preservation, and the use of chemical fertilizers, sprays, and additives are necessary to grow, preserve, and transport sufficient food for the world's human population. Without them many millions would die of starvation.

"It is essential to get your vitamins or minerals only from food."

In truth, the enrichment of foods with vitamins and minerals shares with multiple vitamin and mineral supplementation in pill and capsule form much of the credit for the improved nutritional status so evident in this country since 1940. The agricultural scientists and the scientific farmer alike know that it is not practical or economic to raise hogs or chickens from purely agricultural products alone. They supplement the diet of their animals with a variety of vitamins, minerals, and other nutritionals. Although man does not like to think of himself as governed by similar nutritional rules as the farm animals we could learn and profit much by following what the scientific farmer practices rather than listen to what some agricultural scientists recommend for human consumption. Vitamin and mineral supplementation, whether by food enrichment and fortification or by multiple-vitamin-and-mineral preparations, or both, are indicated whenever a satisfactory diet *cannot* or *will not* be consumed regularly. Overeating is a frequent nutritional fault in America. Overeating leads only to obesity, but our chemical and pharmaceutical industry provides a practical method by which the nutritionally uninformed, as well as the nutrition expert, can obtain with great

certainty sufficient quantities of the essential vitamins and minerals without overeating.

Conditioned Deficiencies

The prevention of conditioned nutritional deficiencies due to illness and stress factors lies almost entirely in the hands of the practicing physician and surgeon. The first consideration is, of course, food—that is, provision of sufficient calories and protein to prevent or minimize a negative nitrogen balance. If the gastrointestinal tract is willing and able, give the best possible diet plus extra sources of protein and calories, such as the various protein-carbohydrate mixtures, plus either a therapeutic-formula or stress-formula vitamin capsule twice daily. When the gastrointestinal tract is unable or unwilling, resort must be made to parenteral feedings of calories in the form of glucose and of amino acids and of electrolytes. But whatever form of parenteral feeding is resorted to, it is necessary to fortify it with the water-soluble vitamins and to discontinue parenteral feeding as soon as the intestinal tract can adequately take over.

THERAPEUTIC USE OF VITAMINS

Successful treatment of vitamin deficiencies involves many factors other than giving vitamins. It involves careful diagnosis. It involves treatment and whenever possible the elimination of the stress or conditioning factors. It involves symptomatic treatment for a comfortable patient is of great aid to recovery. It finally involves nutritional therapy in sufficient amounts over a sufficient period of time to evoke maximal reversal of the nutritional syndrome.

Adequate nutritional therapy does not consist in giving only the nutrients of which a deficiency is clinically manifest. Most deficiencies are multiple and deficiencies clinically manifest are generally associated with tissue deficiencies not yet clinically manifest. Adequate therapy therefore requires administration of sufficient amounts of the specific nutrients over a long enough time to obtain maximal reversal of the manifest lesions and also the restoration of tissues and biochemical normality in all the essential nutrients. This can best be accomplished by the judicious combination of diet, the essential vitamins, and specific therapy.

The best diet possible under the conditions is essential. This means a full, nutritious, high-protein diet administered in amounts sufficient to meet the calorie and nitrogen requirements of the patient.

Mixed-vitamin therapy is the second essential. Two capsules daily of either a therapeutic formula or of the stress formula may be given till the patient is well on the way to recovery. After that give once a day until the patient is able to return to work. Then one of the supplemental formulas is generally advisable, especially if the patient is unable to have a diet adequate in every respect.

To this basic therapy of diet and mixed essential vitamins are added *extra amounts of the specific nutritients* as indicated by the deficiency manifest. Thus if there are lesions of vitamin A deficiency 50,000 to 150,000 units of this vitamin are given. Similarly, for their specific lesions 10 to 20 mg. or even 100 mg. of thiamine; 5 to 25 mg. of riboflavin; 100 to 1000 mg. of niacinamide; 500 to 3000 mg. of ascorbic acid; 10 to 20 mg. of folic acid; 30 to 1000 μg. of vitamin B_{12}; and 10 to 50 mg. of pyridoxine are administered. In acute deficiencies this treatment may be required for only days or at most weeks; for chronic deficiencies treatment may be required for much longer periods.

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DISCUSSION

Dr. Garfield G. Duncan (Philadelphia, Pa.): The fact that deficiency diseases occur throughout the world and in the wealthy as well as the poor has been emphasized. It is an interesting problem to solve as to what will be done for such nations as Japan and India. At the present rate of increase, Japan will double her population of 84 million people in four islands slightly smaller than the State of California in less than 33 years. How her nutritional needs are to be cared for is not apparent.

A clinical case of malnutrition in point might be dramatized in an incident

that happened on Goodenough Island in 1943. While examining a patient critically ill with scrub typhus, I noted that a ward attendant brought a tray to the bed next to the patient that I was examining. The patient who received the tray had meningoencephalitis, due to the scrub typhus. He was quite unconscious when the tray was placed beside the bed, and in twenty minutes the attendant returned, looked at the patient and then at the tray and said, "You didn't eat much, did you, Buddy?" and took the tray away.

I just wondered how often such incidents were happening to a lesser degree, in our own hospitals and so, on return to civilian life, we made a dietary survey at the Pennsylvania Hospital. We weighed all of the food that went to every patient for two successive days on the Medical Division, the Surgical Division, and the Obstetrical and Gynecologic Division.

Some seventy-eight patients were surveyed in the Medical Division. Of the 10 with the lowest food intake one patient with luetic aortitis consumed an average of 17 Gm. of protein per day; one with bronchiectasis, 29 Gm. per day; another with luetic aortitis, 39 Gm. of protein per day; and so on. The 10 patients with the lowest food intake, out of 78, had diets grossly deficient in protein and in total calories. Only 1 in these 10 patients had an intake of over 1000 calories. Evaluation of the vitamin intake revealed deficiencies that were equally pronounced. I believe these dietary insufficiencies are of great significance, but notably in cases of bronchiectasis. We had only 2 patients in the hospital with bronchiectasis at the time. One had a protein intake of 29 Gm. and the other 49 Gm.—barely more protein than each was getting rid of in his sputum each day. Surely, this state of nutrition in patients with bronchiectasis contributes adversely—and to a marked degree —to their progress.

I would, in closing, like to emphasize what Dr. Jolliffe has said; first, that these disturbances in nutrition should be identified; second, that appropriate measures should be taken to correct them and to prevent them in the future; and third, and fundamentally important, is the follow-through. The mere diagnosis and prescription of appropriate dietary management is no assurance whatever that the patient will have an adequate intake, and unless we are nutritionally conscious, continuously from day to day, such things will occur and are occurring, I am sure, in the wards of your hospitals as it is occurring in ours.

Dr. John H. Browe (Albany, N. Y.): I would like to offer these few comments for your consideration with regard to dietary management, more in the setting of the doctor's office and the patient in his own home than in the hospital, but I think the remarks are equally applicable.

First of all, the physician needs to know what the nutrients are that his patient needs. Once he has come to that decision, he then has to see that his nutrient prescription is filled—in this instance, that the patient, through one means or another, consumes these nutrients. The doctor may prefer to in-

struct the patient himself. He should know what the patient is in the habit of consuming. He should then compare that with the nutrient prescription and then modify the patient's everyday dietary pattern to meet the prescription. This also means that the physician must have a knowledge of food composition. This is perhaps one of the greatest needs today, not only on the part of the physician but on the part of everyone working in nutrition.

On the other hand, the physician may choose to have a dietitian, nutritionist, or some other professional person follow through with the patient on the dietary prescription. I can assure you from many sad incidents that a prescription such as a "diabetic diet," a "weight-reduction diet," a "low sodium diet," a "low salt diet," or whatnot, is quite meaningless for the professional person to have as a basis to work on with the patient. The dietitian and nutritionist need the prescription in terms of calories and nutrients and whatever modifications the physician wants. She would then follow through with the patient along the same lines as were indicated when the physician instructed the patient himself.

It is important to have an understanding of the obstacles that the patient faces in trying to change his pattern of eating. One hindrance may be insufficient information as to the reasons why he should change it. Another reason may be because he does not wish to or cannot comfortably—and we are supposed to keep patients comfortable—follow a more or less rigid routine without an opportunity for variety. He may not have the intelligence to follow a complicated regimen. He may not have the money. There are numerous people on welfare, even in these days, and there are many others not on welfare whose incomes are as low as or lower than those provided by welfare. There are also people whose incomes are quite adequate but who put a higher value on other things than on their own personal health and nutrition. In a sense, too, they are on a low food budget.

All these things have to be taken into consideration in trying to follow the dietary prescription. Oftentimes, this is extremely important.

Nutrition and Metabolism In Relation to Neurology And Psychiatry

DOUGLAS GORDON CAMPBELL, M.D.

DISEASES OF THE NERVOUS SYSTEM—so-called organic neurology—are, at least in their overt clinical form, relatively clear-cut entities involving microscopic and macroscopic lesions, eponymous for the clinical syndromes in which they are found. A few neurologic diseases, such as certain convulsive disorders and neuroendocrine syndromes, show a disconcerting lack of morphologic lesions, and for these we assume a pathogenetic substrate at submicroscopic or biochemical levels of structural change. Psychiatric disorders, on the other hand, with the exception of psychoses associated with organic brain pathology, are conspicuously lacking in cellular pathology from which could be derived the comforts of a Virchovian nosology. These psychiatric disorders, occupying well over 50 per cent of our hospital beds and, in varying proportion, initiating or prolonging much more than half of all human illnesses, are uniquely human in incidence (their appearance in animals being largely a product of human intervention, as in husbandry or experimentation, etc.) according to current theories of psychopathology, and are now chiefly regarded as the consequence of disturbances in human interpersonal relationships. Originating, at least in our era, from the penetrating studies of personal life histories by Freud and his contemporaries, psychopathology has undergone a florid verbalistic development paralleled only by the exuberant speculations of the monastic ecclesiasts of the Middle Ages. Let us remember, however, that Freud himself was a thoroughly trained neurologist with biochemical inclinations who, realizing the limitations of the medical sciences of his day, constructed an entirely

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From the Department of Psychiatry, University of California Medical School, San Francisco, Calif.

hypothetical system—his "metapsychology"—in an attempt to explain normal and deviant human behavior and the empirical problems of therapy. Freud himself expressed the hope that the neurologic sciences would some time in the future find the efficient causes of psychiatric disorder in disturbed cellular pathology and that treatment of the neuroses by cumbersome empirical methods, including psychoanalysis, would be replaced by precise biochemical technics.

Multidisciplinary Approach to Disease

The gulf between the peninsula of the so-called "organic," Virchovian pathology and the huge continent of so-called "functional or psychogenic" disorder reflects the dualistic separation of body and mind, a dichotomy which still hampers the medical sciences. It can be bridged only by the multidisciplined collaboration of clinicians and those biological scientists who concern themselves with submicroscopic or physicochemical aspects of living material, as exemplified by conferences such as this. Already such bridges are under construction with materials from neurology and endocrinology, the physiochemistry of homeostasis, the biographic revelations of psychoanalysis, socio-anthropologic studies of the dynamics of group behavior, and human ecology. Finally, these building materials for a unified theory of man and his diseases may be welded together by such holistic structural concepts as Selye's general adaptation syndrome, Wiener's cybernetics, and Korzybski's general semantics.

SIGNIFICATION IN NUTRITION

Human nutrition is a much more complex subject than animal nutrition. Another dimension is involved, which is due to the fact that quite basic intracellular and intercellular mechanisms of communication have been elaborated into complex systems of representation and communication which organize human individuals into groups called cultures. Nutrients are not just biochemical entities, the selection and ingestion of which are determined by tropistic and reflex mechanisms serving biologic survival, as occurs in subhuman species; at the human level nutrients are, in addition, forms of representation or symbols, fraught with meanings which have been determined by individual or cultural experience, and thereby subject to acceptance or rejection with sometimes scant regard for their metabolic merits. This complicating new dimension in human nutrition is a consequence of the neocortical development of the human brain which provides for the storage and transmission of human

experience across generations by means of symbol systems, thereby structuring our cultural milieu. Because the human nervous system has this unique capacity to make and store forms of representation (symbols) which govern conditional responses (semantic reactions to symbols) it is peculiarly sensitive to its own past experience and to communications from other sources.[1] Within wide limits, but with little awareness, man produces an external milieu of nutrients and attitudes toward them that, for better or worse, affects his internal metabolic milieu. Only during fetal life do the basic biologic demands of nutriture function automatically; even then, of course, they are subject to the vicissitudes of the mother's nutrition.

Food as Conditioners in Childhood

For the human infant each feeding experience, every foodstuff, is neurologically linked at subcortical levels of integration with coincident, conditioning experiences of pleasure or pain which are determined by many other factors than adequacy or inadequacy of the milk. Since the baby is fed by a nursing mother or her surrogate, the nursing experience is actually a social experience and the whole process involving satisfaction or frustration, security or insecurity, love or hate, may come to be represented, symbolically, by some part of the total situation. Thus of an item of food, its temperature, texture, and taste, its adequacy to meet the immediate hungers of the child, the bodily characteristics such as warmth and odor of the nurse, her rhythms of pulse and respiration, and physical characteristics such as light and noise in the surroundings, to mention but a few of the many stimuli impinging on the baby's nervous system during hunger, feeding, and satiety, may, especially when repeated, condition the baby's subsequent nutritional behavior. Hunger, originating from the metabolic needs of various tissues, may be negatively conditioned by fear, hate, and the real or imaginary deprivation of personal attention or love to produce such morbid states as marasmus in infants or anorexia nervosa in adults. Or it may be deviated into voracious or capricious forms of appetite resulting in obesity, alcoholism, and other addictions, into a wide range of psychosomatic gastrointestinal disorders and other varieties of malnutrition. The psychiatric study of those cases of malnutrition resulting from the inappropriate selection and consumption of food frequently reveals their source in emotional disturbances connected with the feeding of infants and children. In corollary, happy, nutritionally adequate feeding experiences in infancy and childhood are the best assurance for optimum nutritional

and mental health in later life. I shall not take the time to emphasize the importance of the nutritional care of mothers and the breast nursing of infants.

Food as Cultural Expressions

Not only are psychophysiologic reactions toward foods and feeding conditioned by unique personal experiences arising from the vicissitudes of the emotionally charged family relationships of childhood, but also by the collective representations of the culture as in racial, national, and religious nutritional practices or, nowadays, the high-pressure merchandising technics of food purveyors. Since these conditioning mechanisms operate automatically, below levels of conscious awareness, it is almost as difficult to change feeding habits as to alter political or religious beliefs. Foodstuffs and their preparation and ingestion have become associated to the point of identification with individual and collective notions concerning masculinity versus femininity, purity versus filth, spirituality or sin, childhood, maturity, disease, and old age. Pavlov pointed out that man is much more influenced by words and other symbols than by facts of scientific objectivity. For these reasons every human activity connected with the production, storage, marketing, preparation, and serving of foodstuffs conditions the ingestion and absorption of nutrients and must be evaluated as an important factor in all problems of human nutrition.[2, 3]

Effects on Neurophysiologic Mechanisms

The mechanisms of digestion, absorption, transport, and intermediate metabolism are also affected by these psychosomatic mechanisms. Chewing and swallowing, gastric and intestinal digestion, absorption by the mucous membrane of the gut, and transportation by the vascular system are all governed by central and autonomic cerebral stations and nerve pathways which regulate varieties of muscular and glandular effectors. The conditioning of these mechanisms by psychosocial stimuli has been amply demonstrated by psychoanalytic investigation and clinical experiment. The enzyme systems of intermediate metabolism, as for example in the liver, are directly affected by the nutrients delivered to them. Consequently they too are indirectly modified by neuropsychic and neurophysiologic reactions governing the consumption and absorption of essential nutrients.

NUTRITION AND THE NERVOUS SYSTEM

No other organ of the human body is so involved with all phases of nutrition as the nervous system. Like any other tissue of the body the nervous system has its own nutritional requirements. If these are not provided by the very systems, organs, cells and physicochemical mechanisms it governs, reversible or irreversible damage to its own structure and function will ensue. The secondary impairment of neuropsychic and neurophysiologic functions resulting from disturbances of intermediate metabolism within the nervous system itself may establish vicious circles which further disturb the metabolic activities of its extraneural supporting tissues, such as the exocrine and endocrine glands, the blood-vascular system, etc., to produce systemic disease, general inanition, and eventual death. Since malnutriture of the nervous system may be both a consequence and a cause of the disordered metabolism of other tissues, the reciprocal relationship between the nervous system and other functioning parts of the bodily economy can only be evaluated in the settings of human culture which human nervous systems have themselves produced. This circularity of human nutritional problems, and their multidimensionality, require integrative methods of investigation.

Nutriture of Nerves

The governing functions of the nervous system which regulate all internal and external activities of the organism are the consequence of the extreme degree of specialization of nerve tissue for integration. Integration, however, depends upon communication; communication depends upon those basic physicochemical properties of protoplasm which provide discriminating responses to various modalities of stimulation, transmission of the centrally modified effects of such stimulation, and the activation at varying times and distances of muscular and glandular effector structures. The differentiation of these specialized functions has been achieved at the cost of other cellular functions, such as reproduction, which is completely absent in nerve tissue, and regeneration, which has been greatly restricted. A unique metabolism has developed in nerve tissue to provide extremely labile energy transformations subserving responsiveness and transmission together with energy-binding or storage circuits for the retention and delayed discharge of conditional responses governed by past experience, present events, and future contingencies. This highly specialized metabolism of neurons is apparently completely depen-

dent upon less-differentiated supportive tissues. The immediate services of glial cells, selective filtration by the blood-brain barrier, transportation by the blood-vascular system, nutrient supplies from the liver and other glands, the absorptive and digestive functions of the gastrointestinal tract, and the availability of crude nutrients, obtainable from the external milieu within the conditions of human socio-economic life, are equally important factors for nutriture of the nervous system.

Brain Metabolism

Current knowledge of brain metabolism is comparatively meager. The trophic unit of nerve tissue—the neuron—whether central or peripheral in location, is ectodermal in origin but intimately dependent upon glial cells deriving from both ectodermal and mesodermal sources. The delicate pia-glial membrane—or blood-brain barrier (also originating from the same embryonic tissues)—acts as a semi-permeable membrane between capillary blood and the interstitial fluids of the brain. The analysis of the functions of these cellular elements and their interrelations poses the most taxing problems in neurophysiology and biochemistry. In vitro experimentation must be interpreted with great caution. In vivo findings may be conditioned by unrecognized factors deriving from heredity, development, pre-existing diseases, and, in the human, from the stress of clinical observation and other neuropsychic conflicts of which the patient himself is usually not aware.

Glucose and Oxygen

We know that the nervous system is predominantly dependent upon blood sugar and oxygen. Deficiencies of either lead to a wide spectrum of clinical syndromes. While chemical mechanisms for energy transformations have been elucidated by combinations of the Embden-Meyerhof glycolysis and the Krebs citric-acid cycle, it is not known precisely which phases take place in neurons themselves and which in their supporting tissues. Indeed, recent work indicates that the phosphorylation of glucose, like that of thiamine, takes place in the liver rather than in the brain. Glutamic acid, long assumed to be an essential nutrient of nerve tissue, has been demonstrated to be principally a deaminating agent.[4]

Other Essentials

Impressive as the dependency of brain tissue upon an adequate oxygen supply and the metabolism of glucose may be, the anabolism

and catabolism of other nutrients must also be important; for the variations in Nissl substance and mitochondria, the growth and regeneration of axis cylinders and myelin sheaths, and so on, attest an active metabolism requiring nitrogenous and fatty materials, as also do the labile enzyme systems upon which the energy exchanges of neuronal functions depend.[5] Certain vitamins, especially those of the B-group which are essential to carbohydrate metabolism, must not only be in adequate supply from the diet but require the production of their coenzymes. Minerals, such as iron, calcium, phosphorus, copper, cobalt, sodium, potassium, and many others, are required by nerve tissue for its enzyme systems and for maintenance of the electrolyte balance of its fluid media. Until further research clarifies the obscurities of intermediate metabolism of nerve tissue itself, the only useful clinical approach toward maintaining or restoring the healthy nutriture of the brain is to apply our more advanced knowledge of the conditions governing the metabolic functions of those systems, organs, and cells which supply the nervous system with nutrients or eliminate its metabolites.

MALNUTRITION AND THE NERVOUS SYSTEM

Malnutrition of the nervous system is entirely of the conditioned type. It is secondary to any factors interfering with the ingestion, absorption, and utilization of essential nutrients or factors which increase their requirement, destruction, or elimination. This is of great importance for clinical neurology and psychiatry, since the great majority of patients with illnesses in these fields show signs of malnutrition. Furthermore, from the point of view of therapy, the routine prescription of a "well-balanced" diet, (that gratuitous assumption of patient and physician alike!), even supplemented by vitamins and minerals, will be ineffective if the conditions interfering with the destiny of essential nutrients are not alleviated. Unfortunately, neurologists and psychiatrists have, in the main, been too much influenced by the verbally defined limits of their specialities to pay sufficient attention to the nutriture of their patients. This is especially true of psychiatrists, some of whom seem to have repressed their medical training in their zeal for unalloyed psychogenetic theories, while others leave the physical care of their patients to medical colleagues in other fields of specialization. Neurologists, while diligently investigating the metabolic disorders of the nervous system as if it existed in isolation, have usually disregarded extraneural conditioning factors.

Conditioned-Malnutrition Cycle

Conditioned malnutrition, so well analyzed and systematized by Jolliffe, may be both cause and effect in neurologic and psychiatric disorders.[6] Invariably, the pathogenetic effects of malnutriture of the nervous system are circular. I do not intend to pun by likening such reciprocating action within the nervous system to the "feedback" mechanisms of servo systems; for no matter what the precipitating cause of malnutrition in a given illness may be, the sequence of anorexia, digestive and absorptive insufficiency, disturbances of intermediate metabolism, etc., lead to depressed neuropsychic and neurophysiologic functions. Certain strictly neurologic diseases, produced by a wide range of pathogenetic agencies, may interfere directly with the motor mechanisms of feeding, as in the various central or peripheral palsies ranging from traumatic destruction to inflammatory and degenerative lesions. Neuroendocrine disorders may profoundly disturb the nutriture of target organs and of the body as a whole, as in pituitary cachexia, acromegaly and gigantism, thyroid and adrenocortical syndromes. Lesions of the diencephalon, or other stations on autonomic pathways, may not only produce bizarre disturbances of ingestion (e.g., hyperphagia) but disintegrate the functioning of exocrine and endocrine glands (e.g., hyperinsulinism) and the smooth muscle of the gastrointestinal and vascular systems. These are but a few of the reciprocating mechanisms which, if not recognized and appropriately treated may initiate, prolong or ultimately destroy the capacities of the nervous system to sustain life.

Psychiatric illnesses, apart from so-called "normal" cultural behavior referred to earlier, may not only produce, but also be maintained and aggravated by, such vicious circles compounded from conditioned malnutrition and even terminate in needless death therefrom.

Specific Effects of Psychiatric Illnesses

Certain neuropsychiatric disorders have a more specific effect upon dietary intake. The feeding disturbances of infancy and childhood are frequently the expressions of depression due to deprivation of love, as in marasmus.[7] It has been repeatedly demonstrated that bottle-fed infants should be nursed in contact with the body of the food donor and that visual, auditory, and tactile relationships with people should accompany the feeding of all children so that the fundamental relationship of nutritive and social activities will be properly established. Etymologically the word *companion* means a person with whom one

eats the same bread, and the word *communion*, with its meaning of sharing, is symbolized by two or more people eating the same food.[8] Other feeding disturbances in the forms of specific cravings or aversions and disorders of ingestion, such as dysphagia or regurgitation, are due to conditional reactions produced by the association of strong emotions with feeding activities.

Thus both hyper- and hypoalimentation may represent the indulgence or repudiation of sexual cravings, the acceptance or rejection of social relationships, love or hate. Anxiety originating from the insecurities of childhood and reactivated by the social stresses of adolescence, maturity, and old age manifests itself in various psychoneurotic and psychotic syndromes in which nutritional disturbances may be prominent. Anorexia nervosa and obesity are only extreme examples of psychologically conditioned malnutrition. Food faddism, a common source of deficiency states, is usually the symbolic expression of sexual and aggressive drives and defenses against them. Bizarre habits of oral ingestion, disturbances of deglutition, periodic fasting, and negativistic refusal to eat or drink occur in psychoneurotic states such as hysteria and obsessive-compulsive neurosis, and in the major psychoses. In all these conditions foods and feeding have acquired meanings which sometimes can only be revealed by the painstaking methods of psychoanalysis before the patient can be freed from their harmful conditioning effect upon his nutrition.[9–12]

Inhibitory and Excitatory Effects of Anxiety

Many psychiatric illnesses, because of the excessive amounts of anxiety generated from the real or imagined stress of disturbed interpersonal relationships, show pathologic states of muscular tension and humoral function. These somatic expressions of anxiety may produce recognizable psychosomatic syndromes or they may be covert because of the greater clinical prominence (and interest in) neuropsychic phenomena, such as obsessive-compulsive behavior, phobias, delusions, hallucinations, and the like, as in many psychoneurotic and psychotic reaction types. Obviously, any emotional interference with gastrointestinal functions can impede or suspend digestion and absorption, thus depriving the liver of essential nutrients for processing and redistribution to other internal tissues.

And neuroendocrine excitations or inhibitions can cause mild or severe disturbances of homeostasis with repercussions on other tissues including the nervous system itself. This is particularly of interest in connection with the pituitary-adrenal axis, where deficiency or excess

of ACTH and ACH produce reactions recognizable as alarm, resistance, and collapse, or their admixture. Emotional reactions to external or internal stimuli may increase the nutritive requirements of the body or certain of its organs by their somatization, as in vascular hypertension or frenetic hypermotility. The excessive destruction or elimination of nutrients may be brought about by mechanisms of corticothalamic stimulation or depression affecting lower neural stations, their efferent pathways and effectors. Malnutrition, whether initiated by the physiologic expression of anxiety or arising from extrinsic causes, will itself produce more anxiety, since awareness of the physically incapacitating effects of inanition constitutes a further threat to survival.[14]

Extrinsic Causes of Malnutrition

In Medicine

Before leaving the subject of neurologic and psychiatric sources of conditioned malnutrition and its reciprocal effects upon the nervous system, mention must be made of some adventitious causes of malnutriture resulting from medical or surgical intervention; i.e. iatrogenic causes of malnutrition. The underfeeding of psychiatric and neurologic patients is commonplace, favors chronicity, and hastens the breakdown of adaptive mechanisms to disease with sometimes fatal consequences. Underfeeding is a result less of medical ignorance than of an unwitting failure to apply known nutritional science because of the influence of medical tradition, folklore, resistances of patients and the inertia of hospital administrators, dietitians, and so on.

Another source of malnutrition is the excessive use of pharmacologic agents in neurologic and psychiatric practice. Many drugs are antimetabolites and produce their effects by interfering with the enzyme systems of cellular respiration and cognate metabolic processes in nerve cells or their supporting tissues. The promiscuous use of barbiturates and other sedatives, stimulants such as amphetamine, or antispasmodics and analeptics, etc., in neuropsychiatric disorders not only impedes normal metabolism but may precipitate nutritional crises, especially if the detoxifying functions of the liver are subnormal. The treatment of intercurrent infections of the nervous system or peripheral tissues by sulfonamides and antibiotics, arsenicals, bismuth, and mercury also impairs normal metabolic processes upon which both liver and nervous system are dependent.[15]

In Industry

Other manmade sources of insidious self-destruction through toxic damage to the extraneural or intrinsic mechanisms of nutrition of the nervous system are the use of chemicals in the food industry and pollution of the air by industrial waste products. Recently there has been increasing evidence that chemicals employed as detergents, dyes, bleaches, and preservatives in the processing of commercial foodstuffs may have toxic effects, and there is no longer any doubt that the widespread use of pesticides in the field or in the home may lead to dangerous concentration of potent enzyme inhibitors in dietary staples. DDT, chlordane, and other chlorinated hydrocarbons may damage the enzyme systems of any cell of the body, and parathion is a specific neurotoxin. Not only are these toxic agents virtually unavoidable in common market foods but they are extremely difficult to eliminate from the body once ingested.

In this connection it is of clinical importance to know that DDT, the most commonly used domestic insecticide, is bound in fatty tissue, with the consequence that the strenuous reducing diets that are the fashion today, particularly in psychoneurotic characters, may release toxic doses of DDT as patients consume their own fat. Thus both the excessive consumption of contaminated animal fats or the too rapid destruction of toxic human fat, due to starvation from any cause, may produce DDT poisoning.

There are many other covert forms of poisoning by antimetabolites which are products of our industrial civilization: coal tar products in "smog," metals and fumes from paints, cleaning fluids, etc., are but a few examples.[16]

UTILIZATION OF NUTRIENTS

The utilization of nutrients required by the nervous system depends upon the integration of the mechanisms of intermediate metabolism occurring in glandular and other tissues. While no one phase of these interlinked biochemical processes may be considered more essential than another, it is nevertheless evident that the liver plays a major role not only in the processing of brain nutrients but also in their storage. *This means that any causes of hepatic dysfunction may interfere with the metabolism of the nervous system.* The liver is primarily dependent upon the gastrointestinal tract for supplies, and it is therefore subject to the same conditioning factors that regulate appetite, ingestion, digestion, and absorption. Liver metabolism is under direct autonomic control via the splanchnic plexus and under

indirect control via the neurohumoral system in which pituitary, thyroid, adrenal, gonadal, and pancreatic hormones play important roles.

Role of the Liver

The detoxifying functions of the liver have long been known: the biochemical mechanisms (responsible for conjugation, oxidation, reduction, methylation, and acetylation) require adequate and at times increased supplies of essential nutrients. This is also true for the hepatic production of antibodies. Although the liver has enormous regenerative powers, as evidenced by spectacular recoveries from acute necrosis and prolonged survival in chronic cirrhosis, they are dependent upon adequate dietary supplies and an intact neurohumoral apparatus. Malnutriture of the liver makes it more vulnerable to endogenous and exogenous toxins. This may explain why quite small dosage of certain drugs or slight and transient infections, toxemias, deficiencies of essential nutrients, or relatively moderate stress from any source may precipitate acute illness in patients with the superficial appearance of good health but whose nutrition is marginal.[17; 18]

The role of the liver in lipid and steroid metabolism is of great importance in neurology and psychiatry. While the direct effects of pathologic fat metabolism in nerve tissues—the lipoidoses—are fortunately rare, the indirect effects from atheromatous degeneration of blood vessels in the brain or peripheral organs are increasingly common. The impaired synthesis of lipoproteins by nerve cells, or anoxia and hypoglycemic conditions due to circulatory collapse, may be consequences of inadequate fat metabolism in which the liver plays an important role. The destruction of androgens and estrogens must be effectively carried out by the liver, since accumulation of these hormones may contribute to not only a wide variety of pathologic tissue changes in peripheral organs, but also eventual psychopathological reactions.[19] While these latter disturbances may be due to the direct action of the sex hormones and related steroid on nerve tissue, they are principally the indirect consequence of anxiety produced by sexual impotence in the male, increased desire in the female, and undesirable alterations of bodily constitution such as obesity, hirsutism, and gynecomastia. The metabolism of steroids affects the pituitary-adrenal axis and thus will indirectly influence the general adaptation syndrome initiated by any type of stress. There is little doubt of the contribution of such hepatic dysfunction to states of exhaustion in certain psychiatric and neurologic illnesses.

Of course the liver may produce fatigue and exhaustion by other channels, such as failure to supply enzymes, glucose, and other essential nutrients to the nervous system.

Importance of Adequate Nutritional Support of the Liver

With the liver acting as the principal organ for the chemical transformation (processing) into utilizable forms of brain nutrients and the first line of defense against exogenous and endogenous neurotoxins (including the conjugation of urea from ammonia produced by protein catabolism in the brain and other tissues), its nutriture becomes of paramount importance in the growth, maintenance, and repair of nerve tissue. As far as diet is concerned, a healthy liver can adapt itself to quite wide variations in the proportions of the basic nutrients, provided a minimum of complete proteins is present, together with some fat and minerals. If, however, the liver has been damaged by acute or chronic starvation, by toxemia, by imbalance of various hormones, etc., it will need increased amounts of many nutrients. Lesser, even subclinical, forms of hepatic insufficiency in all probability also require larger amounts of these essential nutrients. Any factors interfering with the utilization of nutrients, such as hypothyroidism or malignant disease, anoxia, or the therapeutic use of anesthetics and other antimetabolic agents, affecting the nutriture of other tissues of the body will put an added strain upon the liver and should be an indication for increased nutritional support. The liver has been called the *porta malorum*; it is unquestionably the principal metabolic gateway to the brain.

DIAGNOSTIC IMPLICATIONS

This account of some currently known nutritional mechanisms determining brain metabolism, and which play a contributing and sometimes prime causal role in nervous and mental diseases, would be even less complete without brief reference to their implications for diagnosis and therapy. Recognition of the malnutriture of the organism or its parts depends not only upon the clinical ability to observe the presenting signs and symptoms of malnutrition either in specific tissues of the body or in total behavior but also upon the nutritional history which, if carefully searched, will reveal the vicissitudes of nutritional health and disease.

In this latter connection the family history reveals the ecologic and hereditary background affecting the developmental potentials of the patient's tissues in fetal life. And the history of the infantile and childhood periods reveal the adequacy of sustenance, the as-

saults by infections, trauma, and psychosocial stress on the structure and function of individual tissues and total organism. Adolescent and adult nutritional stresses arising from disease or starvation should also be sought, together with a searching inquiry into dietary habits and emotional life. Only by the collection and integration of such comprehensive data can we evaluate the present status of a given patient as the exponential product of all nutritional stresses that have gone before. And the analysis of such data from many patients will contribute greatly to unified theories of the etiology of physical and mental disease.[20]

THERAPEUTIC IMPLICATIONS

Therapy is implicit when diagnosis, as Galen maintained, becomes "an account of all things present." Malnutrition of a given patient may appear to be generalized, but it always involves varying degrees of metabolic insufficiencies of his component tissues, since they are affected individually by starvation in different degrees at varying phases of the life history according to hereditary and genetic determinants affecting their growth, thereby determining their reactions to life stresses.

This means that the nutritional therapy of patients should be designed to meet both general and special metabolic requirements. The diet of our anxious patients, whether suffering from overt neurologic disease or from psychiatric illness with its global disturbance of psychosocial functions, should have a broad and more than ample base (to allow for inefficient absorption and utilization, etc.) with the addition of specific metabolic agents, vitamins, lipotropic agents, and the like, which, in the light of our present incomplete knowledge, will meet the needs of particular tissues. An awareness of conditioning factors accessible to therapy will enable the physician to intervene medically, psychiatrically, or even surgically, so that the well-designed dietary nutrients will reach their destinations in intermediate metabolism for the maintenance or restoration of health.[21]

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DISCUSSION

Ivan F. Bennett, M.D. (Coatesville, Pa.): At the Veterans Administration Hospital in Coatesville we are establishing a multidimensional research center, including biochemists, psychologists, and psychiatrists to investigate biochemical deviations in the schizophrenic patient and their possible role in aberrant behavior. With the introduction of hallucinogenic and tranquilizing drugs in psychiatry, we find ourselves in the same position today as the early nutritionists did when it was discovered that certain trace substances called vitamins were essential for plant and animal growth. Just as certain chemical substances in minute amounts can markedly affect the growth of an organism, so it now begins to appear that other chemical substances in minute amounts can markedly affect the behavior of plant and animal organisms. In short, just as there may be a chemistry of growth, there may also be a chemistry of behavior.

LSD-25

The most intriguing of these experimental drugs is the diethylamide of *d*-lysergic acid (LSD-25) which, in mere traces ($\frac{1}{1000}$ mg./kg. in the human), can simulate functional psychoses, notably schizophrenia. This, through its sympathomimetic activity, disrupts the homeostasis of the autonomic nervous system initiating a series of disorganizing events. This is seen first, as described by Hoch, in alterations of perception, bodily sensations, and changes in body image. The interference with time and space sense leads to a general lowering of reality testing and control to which the individual responds with anxiety, tension, and apprehension. Such secondary elaborations as hostility, rage, and paranoid trends are then manifest. Thus, the reaction can resemble a full-blown schizophrenia. The increased resistance of the schizophrenic patient to the effects of LSD-25 was explained by Condrau as possibly due to the endogenous production of a similar substance. The structural similarity between adrenalin and mescaline, another hallucinogen, was

noted by Osmond and Smythies, who suggested the possible formation of a toxic catechol amine from disturbed adrenalin metabolism. Hoffer, in a survey of the hallucinogens, noted that the more important ones, including LSD-25, contained the indole nucleus. From these two observations, the group reasoned that adrenochrome, both an oxidized product of adrenalin and an indole compound, might produce a psychotic reaction. Synthetic adrenochrome did, although this effect has not been duplicated by others (e.g. Rinkel) who feel that the responsible compound is a further oxidation product, adrenoxine. However, this has neither been isolated nor chemically defined as yet.

Indolic Compounds

In common with other investigators, we have become interested in the origin and fate of the indole nucleus and its possible role in the biogenesis of a schizophrenia-producing substance. In this connection, it is important to note that indolic compounds can arise from the metabolism of two well-known amino acids, tyrosine and tryptophan.

Tyrosine-Metabolism Products

First, let us consider the possible origin of indole compounds from tyrosine metabolism. This may arise in the following way. Tyrosine is acted upon by tyrosinase to form DOPA (3,4-dihydroxyphenylalanine). DOPA may follow one of two metabolic pathways. The first pathway would involve its oxidation to DOPA-quinone and the eventual formation of 5,6-dihydroxyindole. The second pathway would involve the formation of either hydroxytyramine or DOPS (3,4-dihydroxyphenylserine), the hydroxytyramine being formed by decarboxylation and the DOPS by oxidation. Either of these compounds could then form noradrenalin, which, upon being methylated by ATP and methionine, would give rise to adrenalin. The action of either tyrosinase or polyphenol oxidase upon adrenalin would then produce adrenochrome, a substance containing the indole nucleus.

The enzyme tyrosinase would thus appear to be implicated through the whole metabolic chain in the formation of indole compounds from tyrosine. Since tyrosinase is a copper containing enzyme, we wonder whether there might be a disturbed copper metabolism in schizophrenia. A search of the literature revealed that Heilmeyer (1941) claimed to have noted an elevated serum copper level in schizophrenia. This is still controversial, since Munch-Petersen (1950) was unable to repeat these results. Because of this, we felt such a determination might be of interest. Our study, involving 32 normal and 63 recently admitted schizophrenic males, showed a mean difference of 14.99 μg./100 cc. serum between these two groups with the schizophrenic group having the higher level of blood serum copper. The standard deviations of the schizophrenic and normal groups were 23.74 and 23.03, respectively. These differences are very significant and would not be expected to occur by chance more than one time out of one hundred ($P < .01$).

Tryptophan-Metabolism Products

The second major pathway for the biogenesis of indoles would appear to be from tryptophan, the only naturally occurring amino acid containing the indole nucleus. Its metabolism excites us for several reasons. There are three routes of tryptophan metabolism by which indole compounds can be formed and which have possible relationships to brain metabolism and mental derangements. One is the classic indoleacetic acid and related indolepyruvic acid pathway which gives rise to indole through the action of bacteria on proteins in the intestine. In this connection, it should be noted that indole-3-acetic acid is identical with heteroauxin, a plant growth hormone stimulating cell elongation and found in human urine. It is possible that the highly controversial toxic factor claimed to be present in the blood serum and urine of schizophrenic patients (detected by growth inhibition of paramecia, l-fibroblasts, *Lupinus albus* seedlings, and tadpoles), may be this compound or an indole structure related to it. The second route is the serotonin pathway which could generate indole compounds known to be hallucinogenic, e.g., tryptamine and bufotenine. Serotonin itself is believed to play an important role in the normal function of the central nervous system, where it is highly concentrated, especially in the hypothalamus. It should be noted that LSD-25 is the most active antiserotonin agent known. The third route is the kynurenine-nicotinic acid pathway with 94 per cent of the nicotinic acid being excreted as N^1-methylnicotinamide. Nicotinic acid itself has been claimed to be of value in the treatment of acute schizophrenia and in the dissolution of an LSD-25-induced psychosis. Its importance in pellagra and as Coenzymes I and II in carbohydrate and nerve metabolism is well established and need not be detailed here.

Metabolism of Indole Compounds

At present, research in our own laboratories in indole metabolism is proceeding along the following lines. First, we are attempting to develop reliable assay methods for indole compounds. We have obtained a considerable amount of data dealing with the Ehrlich benzaldehyde reagent. Secondly, we are engaged in fractionation studies, utilizing paper chromatography, for the detection of indolic compounds in blood and urine of normal individuals and schizophrenic patients. Thirdly, urinary tryptophan and tyrosine tolerance tests on normal subjects and schizophrenic patients are in the process of being tried as a means of unmasking possible aberrations in indole metabolism. Lastly, our biochemists, under the direction of Dr. Herbert Sprince, have worked out a theoretical metabolic pathway by which the diethylamide of lysergic acid could be formed in the human body from metabolites known to arise in a disturbed nicotinic acid metabolism. Many interesting aspects, not only in the field of enzyme chemistry, but also in the realm of practical clinical experimentation present themselves and command our attention at the present time.

Nutritional Problems In Surgery

R. G. RAVDIN, M.D.

There is, of course, no particular field of "surgical" nutrition; the nutrition we are dealing with is precisely the same as that which we meet under various other circumstances. But it is true that the surgeon has some unique opportunities as an applied nutritionist in that his material often comes to him in a depleted condition. He is often presented with, or produces, the stress phenomena in their most pronounced state; many of his patients have gastrointestinal disturbances which complicate their feeding; he has a unique preoccupation with wound healing. In these situations nutrition may well make the difference between success and failure.

In general, the surgeon has an advantage in that he is aiming toward a time when the patient will again be on normal alimentation—he is faced with a relatively short-term problem. It is convenient to consider this in two phases:

- Acute nutritional depletion produced by the disease process itself and by the operative procedure.
- Convalescent nutritional need, after the initial catabolism has subsided and the patient has stabilized and begun the climb to recovery. We shall then touch upon some special applications in special situations.

ACUTE NUTRITIONAL DEPLETION

Although such depletion is commonly encountered, in diseases such as malignancy, ulcerative colitis, and obstructive duodenal ulcer it is also commonly the case that very little time is available for its correction. Indeed, it is often the patient's failure to nourish himself that forces him into the surgeon's hands. Vitamin deficiency states can, and obviously should, be corrected within a short space

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From the University of Pennsylvania Department of Surgery, Philadelphia, Pa.

of time, but the loss of stores of energy and the depletion of parenchymal protein cannot be made up within a brief interval. And the pathologic process cannot wait, or if it can, it may render efforts at improvement fruitless.

Anemic Conditions

It is in this situation that transfusion finds one of its most useful applications. Blood does not act as a nutrient except in the broadest sense. The hypoproteinemia and loss of red cell mass, which characterize the poorly nourished patient so frequently are only a relatively small part of the depletion picture, and their correction will only indirectly benefit the remaining tissues, since these substances enter the metabolic pool very slowly. The diminution in blood volume is the most serious immediate nutritional defect, rendering the patient susceptible to shock, which in turn subjects the viscera to anoxia. A vital organ such as the liver will be more and more sensitive to anoxia as its protein content drops and it becomes increasingly saturated with fat mobilized from the peripheral depots during the period of inanition. Blood volume is simple to determine, and its restoration is the single most important step in the preparation of the undernourished patient for operation.

Electrolyte Loss

A somewhat different situation confronts the surgeon in certain acute illnesses, particularly obstruction of the small intestine, where the patient may have large deficits of electrolytes. Actually, some of the earliest observations of electrolytic disturbances were made in intestinal obstruction, and the first clear demonstration of the value of sodium chloride solutions was also given for this condition. This ground has been well traversed, and we need not go over it again in any detail, except to point out that the recent concept of the "third space," the compartment of the intestinal lumen, has again emphasized that large volumes of electrolyte solutions may be sequestrated in the bowel. In this location they are not lost as vomitus but are nevertheless unavailable to the bodily economy, so that the patient suffers the deleterious effects not only of reduction of blood volume but also of cellular dehydration, with attendant derangements of cellular fractions due to osmotic changes, ion shifts, and the various physiochemical mechanisms of which our understanding is as yet fragmentary. In any event, we must remember that the deficits may

be large. In the presence of physical evidence of dehydration they may be of the magnitude of several liters. The few hours spent in their partial correction are usually warranted.

Effects of Surgery

Now let us look at the nutritional effects of the operative procedure itself. One of the earliest clinical observations on protein metabolism was that postoperative patients developed negative nitrogen balance. This in itself was not surprising, since in many instances no organic nitrogen was supplied during the immediate postoperative period. However, even when nitrogen was supplied, it could not keep pace with the loss. Protein destruction occurred in excess of synthesis, and this increased catabolic rate was roughly proportional to the extent of the injury sustained. We recognize this negative nitrogen balance as one of a group of metabolic changes occurring in the initial phase of the stress phenomenon, mediated by the adrenal in response to pituitary stimulation. But originally it was looked upon as clearly detrimental, and considerable effort was expended to counteract it. Since hypoproteinemia attended so many dangerous complications, should not protein synthesis be forced? Nevertheless, these efforts for the most part proved fruitless, and unless formed protein were introduced intravenously and included in the calculations, nitrogen loss continued greater than nitrogen intake. Formed protein, however, is metabolically inactive. It produced nitrogen equilibrium simply because it could not be eliminated.

It is now evident that efforts to force protein synthesis during the catabolic phase are fruitless, and indeed we can say that this nitrogen deficit is a wholesome sign; far from being disadvantageous, it appears to signal a desirable response. Its absence is an unhealthy prognostic sign, manifested as a rule by the extremely debilitated; whereas it is most prominent in the vigorous and well-nourished. When it fails to occur, other aspects of adrenal failure are likely to be present, especially renal salt loss and decrease in blood pressure. The phenomenon is actually of relatively short duration, averaging 3 to 5 days; when it has abated there is ample opportunity to replenish the protein stores.

Immediate Postoperative Therapy

What are our nutritional responsibilities, then, in this immediate postoperative period? They are relatively simple: (1) We must supply

carbohydrate, which is not stored to any extent in the body and without which the enzyme systems converting energy into chemical work and heat cannot operate and (2) we must maintain the electrolytic environment. We need not supply enough carbohydrate to satisfy the entire energy needs; they will be provided by endogenous fat. The efficiency of glucose metabolism is also impaired during the alarm reaction and it may be impossible to give enough exogenous calories as sugar without exceeding the renal threshold. But we can readily give enough to prevent the body from increasing its protein wastage by converting amino acids into the carbohydrate intermediates. As for the electrolytes, we may simply replace what has been lost. The renal loss of potassium has not yet produced a significant dent in the body stores; the renal loss of sodium and chloride ions has been reduced to a negligible amount almost from the moment of trauma.

We have to consider the losses from other avenues, which often are also negligible but may be tremendous. Gastrointestinal drainage is the most common extrarenal route and may claim 2 or 3 liters of electrolyte solution. An ileostomy may drain as much as 7. The damaged tissue from an area of extensive burn may exchange hundreds of milliequivalents of sodium for potassium, this sodium being again sequestrated and unavailable for bodily needs. One of the significant advances in burn therapy has resulted from the recognition that this source of sodium loss persists well after the loss of plasma has diminished.

NUTRITION IN CONVALESCENCE

Now let us examine the nutritional management of the patient after the few days of intensive metabolic changes have passed. Now, if we have been skillful, or lucky, and things have progressed as we wished, our patient will be ready to look after his own nutritional needs by oral feedings. But we may not be so fortunate. When we are not, either the patient's gastrointestinal tract fails to operate properly, as in a poorly functioning gastrojejunostomy or a prolonged paralytic ileus, or his nutritional needs are so great that he cannot meet them in the course of normal alimentation, as in burns or other severe trauma.

Nonfunctioning Gastrointestinal Tract

In this situation we are forced to resort to other than oral routes to supply nutrients. Of these, the intravenous is far and away the

most suitable, from the point of view of both convenience and the variety of substances that can be introduced.

Protein Hydrolysates

It is now that the protein hydrolysates find their most useful place. To use them before the catabolic phase is over is wasteful of time, effort, and money, but to employ them when the body is prepared to regain its losses has great value in the preservation of parenchymal tissue and lean body mass, provided that the same job cannot be done by mouth. A good deal of work has been done on protein hydrolysates, which we cannot review in detail. We may summarize the data for the most part by saying that such preparations are less efficient than equivalent amounts of untreated protein by mouth; that properly prepared hydrolysates given in large enough amounts will sustain nitrogen balance indefinitely; that they may be directed more to parenchymal use if the hemoglobin and plasma protein levels are maintained by transfusion; and that they will *not* work unless sufficient additional calories can be given so that the amino acids are not used for calorigenic purposes.

Caloric Supply

It is the latter factor that has most limited the use of these solutions. With glucose alone, it is scarcely possible to provide for the needs of an ill individual, and as it is usually used, in 5% solution, they are not met by a very wide margin. Using more concentrated solutions and slower delivery, the deficit is still large. If we add fructose, the utilization of which only partially overlaps with glucose, the gap is narrowed, and by adding alcohol we can, with very assiduous attention, vigorous management, and favorable conditions bring the caloric total to an adequate level. But this is far from satisfactory because we may be limited as to the total quantity of fluid we can safely infuse, or the patient may tolerate the material poorly. In addition, it is difficult to force oneself to make the necessary effort with the feeling that tomorrow or the next day our patient will turn the corner and our problem will solve itself. There is obviously a need for some preparation of high calorigenic value which can be used routinely, and this will obviously be fat. As you know, fat emulsions of small particle size have been used for this purpose and have proved to be well utilized, but they are not ready to be put into general use because the emulsions are not stable and the material tends to be pyrogenic. It will certainly not be long before these

wrinkles are ironed out. Meanwhile, we must settle for a compromise which leaves something to be desired; if we press earnestly enough, we can usually do a reasonably good job.

Electrolyte Replacement

Potassium is lost from the moment of injury and although its loss cannot be prevented, with a reservoir of about 2000 mEq. the renal output can be ignored for a few days. Subsequent potassium depletion will be reflected in pronounced biochemical and physiologic alterations. I will not go into the current controversy as to whether potassium depletion leads to alkalosis or whether the reverse is true, but it is certainly a fact that these phenomena often occur together, and both should be corrected. Potassium replacement should commence about the third or fourth postoperative day and continue again until the needs are met orally.

Vitamins

We may also consider during this period the water-soluble vitamins of the vitamin B groups and ascorbic acid (the fat-soluble vitamins are stored in large enough reserve so that their supply is adequate for the intervals that concern us). There is such general agreement as to the need for vitamins and such widespread use of them that it is difficult to find instances in which their deficiency has proven deleterious. In the European literature, however, in the last several years there have been reports of full-blown postoperative deficiency states. This should not surprise us, since challenges equal to the stress of operation have been used for years to precipitate deficiency states experimentally, and it is well known that stress with its increased metabolic activity increases the need for these coenzymatic substances. Nonetheless, stress alone, without a period of depletion, will not produce a deficiency picture. It is also true that between saturation and the full-blown deficiency state there is no continuous gradation of metabolic alteration. Estimation of actual need on the basis of saturation is likely to lead to highly erroneous conclusions. In effect, if we provide three or four times the minimal daily allowances we are well within safe limits.

Functioning Unreachable Intestinal Tract

Occasionally one is faced with an intestinal tract that will function but cannot be reached. This might be the case after gastric resection when the new stoma fails to open, or in a patient with a duodenal

fistula. Given time, these conditions usually take care of themselves, if nutritional status can be maintained. A feeding jejunostomy is exceedingly helpful in this situation; it is a simple procedure which even a debilitated patient may be expected to tolerate, but it has a bad name on the basis that diarrhea will occur and render it useless. This is an undeserved reputation. Jejunostomy will work well, provided that the materials introduced are not too different from those with which the small intestine is ordinarily confronted. These conditions pertain especially to fat particle size, to osmolarity, and to rate of administration. Whereas ordinary milk gives rise to diarrhea, homogenized milk is almost invariably easily handled, and forms an excellent base for more complex formulas. Simple sugars and easily digested protein may be added; either addition in excess of about 5 per cent will cause trouble, but within this range can generally be managed. Several liters of this material can be given in 24 hours if spaced throughout the period. With such a regimen nutritional needs are readily met.

Insufficient "Normal" Alimentation

The other convalescent situation in which nutrition plays a vital role is that in which "normal" alimentation can be attained but is not sufficient. Here we find an interesting group of patients, in most of which the pathologic process continues well beyond the initial surgical maneuvers. It includes extensive burns; severe trauma; chronic diseases such as tuberculosis and ulcerative colitis, which have led to preoperative malnutrition; common-duct injury with biliary cirrhosis; and bleeding esophageal varices. In any of these diseases, hypoproteinemia is likely to occur, with the attendant dysfunctions of poor wound healing, nonunion of fractures, delayed gastrointestinal motility, edema, and increasing liver impairment.

The problem here centers around augmenting the amounts the patient is inclined to take for himself—driving the daily intake to 4000 or 5000 calories and 2–3 or more Gm. of protein per Kg. of body weight. To the surgeon, accustomed to seizing matters directly and quickly, this tedious business is likely to prove a dreary task, but its performance may well be responsible for the success or failure of the outcome. Here supplemental feeding can be given by vein and the protein hydrolysates are again of value, especially since caloric requirements are likely to be met when the oral route is also available. But the job can often be done entirely by the intestinal tract

by making use of narrow-lumen plastic tubing passed nasogastrically. This material is relatively nonreactive and causes little disturbance and discomfort; it will not serve for suction but is very suitable for instilling solutions of moderate viscosity. Such feeding is best done by night; if given during the day it commonly displaces the regular meals.

SPECIAL PROBLEMS AND MEDICATIONS

Wound Healing

A Special aspect of nutrition pertaining to surgical material is wound healing, a matter of prime concern to surgeons. The major nutritional factors involved in interference with healing are hypoproteinemia, which if we are conscious of it, we are in a position to forestall, and ascorbic acid deficiency, which refers to frank scorbutus and is actually very rare.

Cortisone Therapy

Within recent years, however, the situation has become complicated by the use of cortisone. Although this substance is perhaps on the fringe of the nutritional field proper, it interacts so frequently in metabolic processes that it does not seem inappropriate to comment on the management of patients who have been under cortisone therapy. From the experimental point of view, wound healing is interfered with only by doses well outside the physiologic range, and possibly 3 to 5 times as great as the usual therapeutic dosage. For certain cases, however, larger than what we might call "usual" therapeutic doses have been given; in others, additional factors may be operating to interfere with healing, such as infection, tension, or malnutrition, which may be potentiated by smaller amounts of cortisone than would have any effect under ideal conditions. This may obtain, for example, in ulcerative lesions of the gastrointestinal tract, which have seemed to perforate more readily in cortisone-treated patients. In any event, our experience with cortisone has made us rather leery of it. It appears desirable to reduce the dosage to the physiologic range. On the other hand, it is clearly disastrous to stop it altogether, as this will certainly and promptly precipitate adrenal insufficiency and is far more dangerous than the possibility of wound dehiscence. Somewhere between the fibroblastic inhibition of most advanced antiphlogistic activity and the addisonian crisis, there is presumably safe ground.

Vitamins D and K

A second matter we may touch upon has to do with the special use of vitamins. Vitamin D has a distinct place in the management of postoperative hypoparathyroidism, occurring either as a result of the removal of a functioning parathyroid adenoma or accidental removal of normal tissue at thyroidectomy; you will recall that dehydrotachysterol was originally proposed for this purpose. Of the two actions of the D vitamins—increasing calcium absorption from the bowel and inhibiting phosphate reabsorption in the renal tubule—it possessed predominantly the latter and thus most closely resembled the parathyroid hormone itself. Actually, this refinement is superfluous, and the ergosterols, which are vastly less expensive, can be anticipated to work perfectly well if given in large enough quantities.

Vitamin K also occupies a unique position in the surgeon's armamentarium in the preparation of patients with obstructive jaundice whose prothrombin synthesis has often been interfered with due to failure of absorption of this fat-soluble substance from the bileless gut. Within the last few years we have been interested in the "natural" vitamin K, K_1, which possesses two advantages over the common water-soluble methyl naphthaquinone esters such as Synkayvite and menadione. First, it is strikingly more active in counteracting the hypoprothrombinemia produced by Dicumarol and related coumarins, which are often used as anticoagulants in surgical patients, or may have been employed for other reasons in patients who develop surgical emergencies. Also, K_1 will at times, if given persistently, goad a diseased liver into prothrombin synthesis, and permit an operation on a cirrhotic patient who would otherwise not reach the table.

Extensive Gastrointestinal Resection

As one last consideration, we have the problem of the management of patients who have undergone extensive alterations of their gastrointestinal tract. These include extensive subtotal and total gastrectomy, pancreatectomy, and removal of large amounts of small bowel for mesenteric occlusion. The gastrectomy group is by far the most important numerically. "Gastric cripple" has been used to define some of these individuals who are unable to regain their weight and energy. The interest in modification of the standard resection practiced fairly routinely ten years ago indicates a dissatisfaction with this procedure more than a clear demonstration that the modifica-

tions are superior, and this question remains open. There is some clinical evidence to suggest that restoration of normal continuity, using the duodenum instead of the jejunum for the gastro- or esophagoenterostomy, may offer some advantage. There may also be advantage in retaining more of the gastric reservoir than is done in the usual resection for duodenal ulcer, and protecting the patient by vagotomy. We can only await definitive information along these lines; it is not yet available.

We can say, however, that any of these major defects in the gastrointestinal tract, whether of stomach, pancreas or small bowel, will lead to a real loss of digestive efficiency, and that we may expect to find a significantly higher proportion of undigested nitrogen and fat in the stool than will be found in the normal individual. Various measures can be taken to increase retention—the use of enzymatic replacement, such as pancreatin, and fat emulsifiers, such as Tween 80, as well as feeding predigested material. For the most part, however, the most satisfactory solution is to accept the loss and increase the number of feedings. Digestive efficiency will remain about the same even when the intake is doubled.

We must also watch for anemia, especially following total gastrectomy. Commonly this is due to iron deficiency and is related to the absence of hydrochloric acid, but as more of these patients appear in our 3- and 5-year follow-ups, more macrocytic anemias will be encountered. Here, of course, vitamin B_{12} is specific.

SUMMARY and CONCLUSION

I have attempted to present the broad impact of nutrition in the surgical field, which at times is faced with problems requiring instant solution, as an immediate threat to life, and at times demanding long-term planning lest the patient be lost by default. The surgeon has a right to be proud of those contributions he himself has made. But as we all know, a very great part of the safety and efficiency of modern surgery must be attributed to the advances in nonoperative fields, and of these, nutrition is among the most stimulating and important.

DISCUSSION

Dr. William T. Fitts, Jr. (Philadelphia, Pa.): First, we surgeons agree that nutrition is of vital importance in handling surgical patients. A malnourished patient who comes to operation will have more complications, will

go into shock more easily, will heal more slowly, and is more apt to disrupt his wound than a patient who is well nourished.

Dr. Ravdin emphasized the oral route in feeding surgical patients, and I think we surgeons have been remiss in recent times in taking for granted that we have to feed all patients who have gastrointestinal operations by intravenous feeding for long periods of time. The average patient who has a gastric resection is able to tolerate food by mouth in 46–72 hours, and most patients that we operate on can tolerate oral feedings early. On the other hand, we must try to anticipate those patients who will need a longer period of intravenous therapy, and if we see that they won't be able to take food by mouth by the fifth, sixth, or seventh day, we should begin the type of intravenous feedings which Dr. Ravdin outlined.

We have had a number of poorly nourished patients who have been taking large doses of cortisone for long periods. Dr. Thomas Machella and I have been particularly interested in this group of patients and have tried to determine by consulting various people throughout the country, as well as observing our own patients, the cause of complications following operation, especially the poor wound healing that many of these patients showed.

This group of patients has been on cortisone for long periods of time. They have had diseases which made them malnourished and would predispose them to poor wound healing, even without cortisone. It is probable that it is not the cortisone per se that causes poor wound healing but the fact that these are malnourished patients. Given such a patient that must be operated on, we believe that it is important to increase the cortisone dosage during the immediate stress of operation and the immediate postoperative period and then gradually decrease it to the preoperative level.

I think we surgeons must take a careful nutritional history because only by so doing can we uncover some malnourished patients. A patient with a carcinoma of the right side of the colon may be anemic, (many of these patients are), but we may not recognize the degree of blood loss unless blood-volume determinations are made. Likewise, he will have deficits of vitamins and minerals that we may not have suspected.

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